REMARKS:

In the Office Action dated March 11, 2010, claims 45-92, in the above-identified U.S. patent application were rejected. Reconsideration of the rejections is respectfully requested in view of the above amendments and the following remarks. Claims 1-44 have been canceled without prejudice or disclaimer and claims 45-92 remain in the application.

Claim 45 was rejected under 35 USC §112, second paragraph as indefinite. Claim 45 has been amended as suggested in the office action. In view of this amendment, applicants request that this rejection be withdrawn.

Claims 45-92 were rejected under 35 USC §112, first paragraph as lacking enablement. Applicants respectfully point out that the Office Action has misinterpreted some of the application's data. For example, on page 4, the Examiner quotes page 35 of the specification to support the proposition that the inventors *"were unable to detect RISC activity from antisense siRNA."* The rest of the truncated sentence is "... *presumably because of the high load of single-strand specific ribonucleases"* [in Drosophila extracts]. The rest of the cited paragraph reports only positive findings. The Office Action then erroneously concludes that "the specification makes clear that single-stranded siRNA does not mediate RISC activated cleavage in Drosophila cells". This is incorrect as the experiment referenced in the office action used extracts (not cells) and was explained as likely attributable to RNases. The complete sentence reads as follows "Using D. melanogaster embryo lysate, we were unable to detect RISC activity from antisense siRNA (FIG. 7B), presumably because of the high load of single-strand specific ribonucleases (Elbashir et al. (2001 b), supra)". Moreover, the specification also teaches that "chemical strategies to improve nuclease

systems of single stranded RNA are available." (for example see page 41). Therefore, the statement on page 5 of the office action that "the specification makes it clear that single-stranded siRNA does not mediate RISC-activated target cleavage in *Drosophila* cells" is based on an incorrect interpretation of statements in the application.

The Office Action contends that the Applicant has not shown the claimed method *in vivo* with any type of cells, with molecules which are less than 17 nucleotides or longer than 30 nucleotides in length, with any modification in any position where there are mismatches between the "guide" strand and the target molecule and there was at least one phosphorothioate linkage. In order to advance the examination of the present application, the claims have been amended to recite "in vitro" and "mammalian cell". The in vivo claims will be pursued in a divisional application. Regarding the term "mismatch", the claims have been amended to indicate that the mismatch occurs at the 3' terminus, wherein at least the 15 nucleotides at the 5' terminus are completely complementary to the nucleic acid target molecule. Regarding the term "modification", the claims have been amended to indicate that the modification is a sugar or backbone modified nucleoside at the 3' terminus, wherein at least the 15 nucleotides at the 5' terminus are unmodified. Regarding the language "at least one phosphorothioate linkage", applicants respectfully point out that the phosphorothioate linkage according to the present application does not affect RNA mediating activity. With regard to the length of the molecules, the molecules' length is described as having 14-50 nucleotides on page 11 of the application, and thus there is a clear written description of these molecules. The Office Action also incorrectly presumes that complete complementarity is a necessary predicate for activity. As discussed in the present application, the present inventors have found that single-stranded RNA molecules

having at the 5'-terminus at least 15 nucleotides which are completely complementary to a predetermined target transcript have the desired activity. This is a written description rejection and applicants contend that the molecules recited in the present claims are clearly described in the present application. If the enablement of the molecules according to the present claims is being questioned, applicants request that data or references supporting this position be cited or that official notice be taken regarding the facts that led to the conclusion that the molecules recited in the present claims would not have the desired activity, as part of an enablement rejection. In view of the above discussion and amendments, applicants request that this rejection be withdrawn.

Claims 45-47, 49-50, 63, 65-66 and 92 were rejected under 35 USC §102(a) as anticipated by Tijsterman. Tijsterman discloses a method of cleaving a target nucleic acid in a cell of C. *elegans*. In order to advance the examination, the claims have been amended to recite mammalian cells. However, applicants respectfully point out that Tijsterman teaches primer extension as the mechanism, not RNAi. In fact, the author goes out of his way to avoid invoking an RNA mechanism. Tijsterman suggests that the constructs perform a priming function as asRNA and are not functional equivalents for ssRNAi. asRNA do not substitute for dsRNA (see page 696, column 2, second paragraph). In column 3, the author suggests that *"these asRNA molecules are taking another route to silence gene expression"*. In view of the above amendments and discussion, applicants request that this rejection be withdrawn.

Claims 44-47, 49-50, 63-64, 69-70, 72-73, 86-87 and 92 were rejected under 35 USC §103(a) as unpatentable over Hamilton in view of Vaucheret and Tijsterman. Hamilton and Vaucheret are directed to plant cells and Tijsterman is directed to

C. *elegans*. In order to advance the examination of the present application, the claims have been amended to recite "mammalian cells". The results in mammalian cells would not have been predictable from the results in plant or *C. elegans* cells. *C. elegans* and plants are different from mammalian cells in their RNAi mechanisms as they require RNA-dependent RNA polymerase genes for the process involved in amplifying the trigger dsRNA. These genes are absent from Drosophila or mammals and RNAi is of transient nature with respect to the cells that receive trigger RNAi. In *C. elegans* and plants silencing signals can spread through the entire organism. In view of these differences in the biology and mechanism of RNAi one skilled in the art would not have used results from studies in C. *elegans* to predict that silencing may also be detectable in mammalian systems. In addition, the Office Action indicates on page 8 that a skilled person at the priority date of the present application would have considered it hopeless to use short single-stranded RNA molecules for RNAi. If this statement is correct, then it is even more amazing that the Applicant got it to work. In view of the above amendments and discussion, applicants request that this rejection be withdrawn.

Claims 45-92 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as unpatentable over claims 17-19, 23-25 and 36-37 of co-pending application No. 11/880,355. As discussed above, the Office Action indicates on page 8 that a skilled person at the priority date of the present application would have considered it hopeless to use short single-stranded RNA molecules for RNAi. If this statement is correct, then the presently claimed invention was clearly not obvious. Since the claims in co-pending application No. 11/880,355 have not yet been allowed and may be narrowed prior

to allowance, applicants request that this rejection be held in abeyance until one of the applications is otherwise in condition for allowance.

Applicants respectfully submit that all of claims 45-92 are now in condition for allowance. If it is believed that the application is not in condition for allowance, it is respectfully requested that the undersigned attorney be contacted at the telephone number below.

In the event this paper is not considered to be timely filed, the Applicant respectfully petitions for an appropriate extension of time. Any fee for such an extension together with any additional fees that may be due with respect to this paper, may be charged to Counsel's Deposit Account No. 02-2135.

Respectfully submitted,

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